

IN THE SPECIFICATION:

Please amend the specification as follows.

Please amend paragraph [0001] as follows:

[0001] This application is a continuation of application Serial No. 10/084,868, filed March 1, 2002, which is a continuation-in-part of pending application Serial Number 09/804,040, filed March 13, 2001, which is a continuation-in-part of pending application Serial Number 09/551,614, filed April 17, 2000, now U.S. Patent 6,368,658, which is a continuation-in-part of application Serial Number 09/293,994, filed April 19, 1999, now abandoned.

Please replace paragraph [0025] with the following:

[0025] Specific examples of therapeutic or bioactive agents used in conjunction with the present invention include, for example, pharmaceutically active compounds, proteins, oligonucleotides, ribozymes, anti-sense genes, DNA compacting agents, gene/vector systems (i.e., anything that allows for the uptake and expression of nucleic acids), nucleic acids (including, for example, recombinant nucleic acids; naked DNA, cDNA, RNA; genomic DNA, cDNA or RNA in a non-infectious vector or in a viral vector which may have attached peptide targeting sequences; antisense nucleic acid (RNA or DNA); and DNA chimeras which include gene sequences and encoding for ferry proteins such as membrane translocating sequences ("MTS") and herpes simplex virus-1 ("VP22")), and viral, liposomes and cationic polymers that are selected from a number of types depending on the desired application. For example, biologically active solutes include anti-thrombogenic agents such as heparin, heparin derivatives, urokinase, and PPACK (dextrophenylalanine proline arginine chloromethylketone); prostaglandins, prostacyclins/prostacyclin analogs; antioxidants such as probucol and retinoic acid; angiogenic and anti-angiogenic agents; agents blocking smooth muscle cell proliferation such as rapamycin, angiopeptin, and monoclonal antibodies capable of blocking smooth muscle cell proliferation; anti-inflammatory agents such as dexamethasone, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, acetyl salicylic acid, and mesalamine, lipoxygenase inhibitors; calcium

entry blockers such as verapamil, diltiazem and nifedipine; antineoplastic/antiproliferative/anti-mitotic agents such as paclitaxel, 5-fluorouracil, methotrexate, doxorubicin, daunorubicin, cyclosporine, cisplatin, vinblastine, vincristine, colchicine, epothilones, endostatin, angiostatin, ~~Squalamine~~ squalamine, and thymidine kinase inhibitors; L-arginine; antimicrobials such as triclosan, cephalosporins, aminoglycosides, and ~~nitrofurantoin~~ nitrofurantoin; anesthetic agents such as lidocaine, bupivacaine, and ropivacaine; nitric oxide (NO) donors such as ~~linsidomine~~ lisidomine, molsidomine, NO-protein adducts, NO-polysaccharide adducts, polymeric or oligomeric NO adducts or chemical complexes; anti-coagulants such as D-Phe-Pro-Arg chloromethyl ketone, an RGD peptide-containing compound, heparin, antithrombin compounds, platelet receptor antagonists, anti-thrombin antibodies, anti-platelet receptor antibodies, enoxaparin, hirudin, ~~Warafin~~ warfarin sodium, Dicumarol, aspirin, prostaglandin inhibitors, platelet inhibitors and tick antiplatelet factors; interleukins, interferons, and free radical scavengers; vascular cell growth promoters such as growth factors, growth factor receptor antagonists, transcriptional activators, and translational promoters; vascular cell growth inhibitors such as growth factor inhibitors (e.g., PDGF inhibitor--Trapidil), growth factor receptor antagonists, transcriptional repressors, translational repressors, replication inhibitors, inhibitory antibodies, antibodies directed against growth factors, ~~bifunctional~~ bifunctional molecules consisting of a growth factor and a cytotoxin, bifunctional molecules consisting of an antibody and a cytotoxin; Tyrosine kinase inhibitors, chymase inhibitors, e.g., Tranilast, ACE inhibitors, e.g., Enalapril, MMP inhibitors, (e.g., Ilomastat, Metastat), GP IIb/IIIa inhibitors (e.g., ~~Integrilin~~ Integrilin, abciximab), ~~seratonin antagonist~~ serotonin antagonist, and 5-HT uptake inhibitors; cholesterol-lowering agents; vasodilating agents; agents which interfere with ~~endogenous~~ endogenous vasoactive mechanisms; survival genes which protect against cell death, such as anti-apoptotic Bcl-2 family factors and Akt kinase; and combinations thereof; and beta blockers. These and other compounds may be added to a coating solution, including a coating solution that includes a polymer, using similar methods and routinely tested as set forth in the specification.

Please replace paragraph [0028] with the following:

[0028] When used as a drug matrix layer for localized drug delivery, the polymer coatings of the present invention comprise any material capable of absorbing, adsorbing, entrapping, or otherwise holding the therapeutic agent to be delivered. The material is, for example, hydrophilic, hydrophobic, and/or biodegradable, and is preferably selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, polyethylene oxides, polylactic ~~polyactic~~ glycolic acid copolymers, glycosaminoglycans, polysaccharides, polyesters, polyurethanes, silicones, polyurea, polyacrylate, polyacrylic acid and copolymers, polyorthoesters, polyanhydrides, polycarbonates, polyethylene, polypropylenes, polylactic acids, polystyrene, natural and synthetic rubbers and elastomers such as polyisobutylene, polyisoprene, polybutadiene, including elastomeric copolymers, such as Kraton.RTM., styrene-isobutylene-styrene (SIBS) copolymers styrene-butadiene copolymers; polyglycolic acids, polycaprolactones, polyhydroxybutyrate valerates, polyacrylamides, polyethers, polysaccharides such as cellulose, starch, dextran and alginates; polypeptides and proteins including gelatin, collagen, albumin, fibrin; copolymers of vinyl monomers such as ethylene-vinyl acetate (EVA), polyvinyl ethers, polyvinyl aromatics; other materials such as cyclodextrins, hyaluronic acid and phosphorylcholines; and mixtures and copolymers thereof. Coatings from polymer dispersions such as polyurethane dispersions (BAYHDROL, etc.) and acrylic latex dispersions are also within the scope of the present invention. Preferred polymers include polyurethanes; polyacrylic acid as described in U.S. Pat. No. 5,091,205, the disclosure of which is incorporated herein by reference; and aqueous coating compositions comprising an aqueous dispersion or emulsion of a polymer having organic acid functional groups and a polyfunctional crosslinking agent having functional groups capable of reacting with organic acid groups, as described in U.S. Pat. No. 5,702,754, the disclosure of which is incorporated herein by reference.

Please replace paragraph [0029] with the following:

[0029] The release rate of drugs from drug matrix layers is largely controlled, for example, by variations in the polymer structure and formulation, the diffusion ~~o~~ rate of decomposition or dissolution of the polymer coefficient of the matrix, the solvent composition, the ratio of drug to polymer, potential chemical reactions and interactions between drug and polymer, the thickness of the drug adhesion layers and any barrier layers, and the process parameters, e.g., drying, etc. The coating(s) applied by the methods and apparatuses of the present invention may allow for a controlled release rate of a coating substance with the controlled release rate including both long-term or a burst release where all of the drug is released at a predetermined time.

Please amend paragraph [0031] as follows:

[0031] The coatings of the present invention are applied such that they result in a suitable thickness, depending on the coating material and the purpose for which the coating(s) is applied. As an example, coatings applied for localized drug delivery are typically applied to a thickness of about 1 to 30 microns, preferably about 2 to 20 microns. Very thin coatings, e.g., of about ~~100^oA~~ 100 Å, and much thicker coatings, e.g., more than 30 microns, are also possible. It is also within the scope of the present invention to apply multiple layers of the same or different coating materials, which may perform identical or different functions (e.g., to provide for biocompatibility, to control drug release, etc.).

Please replace paragraph [0041] with the following:

[0041] In yet another alternative embodiment, only one of air streams 161 or 140 are utilized. For example, the airstream 161 is utilized to both suspend the medical devices and introduce the coating material(s) into chamber 120. A cyclical flow of air within the chamber could be provided by varying the velocity of the one air stream across its ~~it's~~ flow pattern, such as, for example, by appropriately configuring the openings in air distribution plate 130.

Please replace paragraph [0042] with the following:

[0042] Although the embodiment 100 making use of the Wurster process is generally preferred for making the coated medical devices of the present invention, any suitable method or apparatus can be used. For example, medical devices may be loaded into a conventional fluidized bed chamber, in which air is introduced into a "bed" or layer of the medical devices from below while the coating material is sprayed onto the fluidized devices from above. In such a process, the medical devices will move randomly within a fluidized bed. Airless and atomized air spray processes are also within the scope of the present invention. Although not required by the present invention, coating within a closed chamber is generally preferred because of the corresponding ability to control the coating processing parameters and the chamber environment. For example, it is advantageous to control processing parameters such as the fluidization air composition, temperature and humidity when coating with drugs or polymers that degrade, oxidize, hydrolyze, etc., upon exposure to specific environments. The present invention may be utilized to coat medical devices with organic-based coating materials. Thus, operating temperatures in at least some embodiments of the apparatuses and methods of the present invention are generally less than 500°C., with some embodiments having an operating temperature of between 0°C. - 200°C. The particular operating temperatures utilized are compatible with the particular coating materials. Thus, operating temperatures compatible with all of the coatings materials disclosed herein can be established and maintained in the apparatuses and methods of the present invention.

Please replace paragraph [0045] with the following:

[0045] Thus, a second embodiment for an apparatus for coating medical devices 200 in accordance with the principles of the present invention is illustrated in FIG. 2. The embodiment of FIG. 2 utilizes a structure similar to that described for the embodiment of FIG. 1, however, in the embodiment of FIG. 2, the coating material may not be dispersed within air stream 161 by nozzle 160. In the embodiment of FIG. 2, both or one of the air streams 161 and 140 are utilized to suspend the medical devices within chamber 120. A coating apparatus 210 is utilized to apply

the coating to the suspended medical devices. ~~Depending~~ ~~Depending~~ upon the particular coating apparatus used, a coating material may be introduced into the coating chamber by the coating apparatus itself, by one or both of air streams 161 and 140, or through any other well-known means that are associated with the particular coating apparatus utilized. For reference purposes, the components for embodiment 200 in FIG. 2 that are common to those of embodiment 100 of FIG. 1 are designated by like reference numerals.

Please replace paragraph [0050] with the following.

[0050] FIG. 3 illustrates a particular alternative embodiment for an apparatus for coating medical devices 300 in accordance with the principles of the present invention where the coating apparatus 210 of FIG. 2 is a plasma coater 305. As described in connection with FIG. 2, in the embodiment of FIG. 3, both or one of the air ~~streams 161~~ ~~streams 161~~ and 140 are utilized to suspend the medical devices within chamber 120; however, a plasma coater 305 is utilized to coat the suspended medical devices. For reference purposes, the components for embodiment 300 in FIG. 3 that are common to those of embodiments 100 and 200 of FIGS. 1 and 2, respectively, are designated by like reference numerals. Plasma coater 305 includes electrodes 310, a matching network 320, and a RF (radio frequency) generator 330. The materials to be coated on the medical devices may be introduced into chamber 120 through either of air streams 161 and/or 140 or through any other means, such as by depositing the coating material on air distribution plate 130 and having the air stream(s) dispense the coating material into the chamber. The coating material(s) are then applied to the medical devices by using plasma coater 305.

Please replace paragraph [0051] with the following:

[0051] In continuing with the discussion of the alternative coating techniques that may be utilized in the present invention, chemical vapor deposition processes are also within the scope of the present invention, ~~employing polymers~~. ~~Polymers~~ such as polyamide, polyimide, parylene, and parylene derivatives, polyalkylene oxide, polyalkylene glycol, polypropylene oxide, silicone

based polymers, polymers of methane, tetrafluoroethylene or tetramethyldisiloxane or polymers from photopolymerizable monomers or combinations thereof.

Please replace paragraph [0070] with the following:

[0070] In situations where the device, part of the device and/or any subsequently coated layers contain one or more therapeutic agents, the methods yield a uniform, well-defined ~~welldefined~~ rate controlling membrane, or a uniformly coated layer incorporating the therapeutic agents. This results in uniform controlled drug release for devices, parts of devices, and/or coatings that contain active components.

Please replace paragraph [0094] with the following:

[0094] As noted above, these coating nozzles can eject a single coating material during the entire coating process or multiple coating materials, each being ejected or delivered at different times or simultaneously, as required, during the coating process. When multiple coatings are being applied, they may be delivered or sprayed to form composite layers, individual layers and any other desired coating configuration. Furthermore, the coating nozzles 630 can each concurrently spray different coating materials so that each medical device 670 can be coated with a different coating dependent ~~dependant~~ upon its location within the coating chamber 610 when the coatings are being delivered. In this configuration the spacing between devices may be increased to reduce the risk of over spray and to control the distribution of coating onto each device.

Please replace paragraph [0111] with the following:

[0111] Numerous (approximately 300 to 600 in this example) NIR stents (Medinol, Tel Aviv) are placed in a Wurster fluidized bed chamber, such as a GPCG-1 (available from Glatt Air Techniques, Ramsey ~~Ramesey~~, N.J.). The stents are each about 9 mm-32 mm in length, about 1.5 mm-3.0 mm in diameter, about 7 mg-35 mg in weight, and about 46-200 mm² in surface area.

Please replace paragraph [0127] with the following:

[0127] The invention includes parallel applications of drug(1)-polymer(1)-solvent(1) and drug(2)-polymer(2)-solvent(2) to eliminate compatibility or solubility issues. Examples include the simultaneous application of (i) cisplatin-hydroxypropyl methyl cellulose-water and paclitaxel-PCL/PLA-chloroform from two different feeds; (ii) albumin or gelatin solution from one feed and glutareddehyde ~~glutarddehyde~~ crosslinker from second feed; and (iii) acrylate monomer solution from one feed and methylene bis acrylamide as crosslinker for the second feed.